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The diuretic effects of SGLT2 inhibitors: A comprehensive review of their specificities and their role in renal protection

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SUMMARY

Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) are new oral glucose-lowering agents that provide cardiovascular and renal protection in both patients with and without type 2 diabetes. Because of their unique mechanism of action, increased glucosuria is associated with osmotic diuresis and some natriuresis, yet the latter seems mostly transient. The potential role of the diuretic effect in overall cardiovascular and renal protection by SGLT2is remains a matter of debate. Precise evaluation of the diuretic effect is not so easy and most studies relied upon indirect estimations that led to divergent results, presumably also explained by different study designs and population characteristics. Everybody agrees upon the fact that SGLT2is are different from other classical diuretics (thiazides and loop diuretics) as they present some favourable properties, i.e. reduced sympathetic activity, preserved potassium balance, lower risk of acute renal injury, decrease of serum uric acid level. The potential role of the diuretic effect of SGLT2is on renal outcomes is still unclear, yet their ability to reduce albuminuria and dampen the risk of heart failure may contribute to improve renal prognosis besides other complex underlying mechanisms. In this comprehensive review we first critically analyse the results obtained with indirect methods that assess a diuretic effect of SGLT2is, second we describe the specificities of the diuretic activity of SGLT2is compared with other classical diuretics, and third we discuss the potential mechanisms by which the diuretic effect of SGLT2is could contribute to the improvement of renal outcomes consistently reported with this innovative amazing pharmacological class.

Introduction

Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) have an increasing place in the management of type 2 diabetes mellitus (T2DM), especially after the demonstration that they can improve both cardiovascular and renal prognosis in patients at high risk of such complications [1–4]. The increased glucosuria resulting from the mode of action of SGLT2is could easily explain a glucose-lowering effect, independent of insulin secretion and/or action, accompanied with some weight loss [5]. Furthermore, these medications are associated not only with osmotic diuresis but also with some, at least transient, natriuresis. These effects could explain a lowering of arterial blood pressure and, even more important from a clinical point of view, a marked reduction in hospitalisation for heart failure, a remarkable effect consistently reported with SGLT2is [1, 4]. These positive effects have been initially demonstrated in patients with T2DM and established cardiovascular disease [6], but later on were also reported in both diabetic and nondiabetic patients with heart failure [7–9]. Of note, SGLT2is improved renal prognosis, as they not only reduced albuminuria but also they attenuated the loss of renal function and reduced the progression to end-stage renal disease and renal death [2, 10]. These favourable effects were observed especially but not only in patients with proteinuria [11], and this renal protection was again demonstrated both in patients with and without T2DM [12]. While the contribution of the diuretic effect of SGLT2is to reduce hospitalisation for heart failure can be quite easily understood [13–15], its potential role to improve renal outcomes is less obvious and remains subject of debate besides several other possible mechanistic explanations [2, 16, 17].

The aims of the present review are *i*) to analyse the results obtained with both direct and indirect methods that assess a diuretic effect of SGLT2is; *ii*) to describe the more favourable specificities of SGLT2is compared with thiazides and loop diuretics; and *iii*) to

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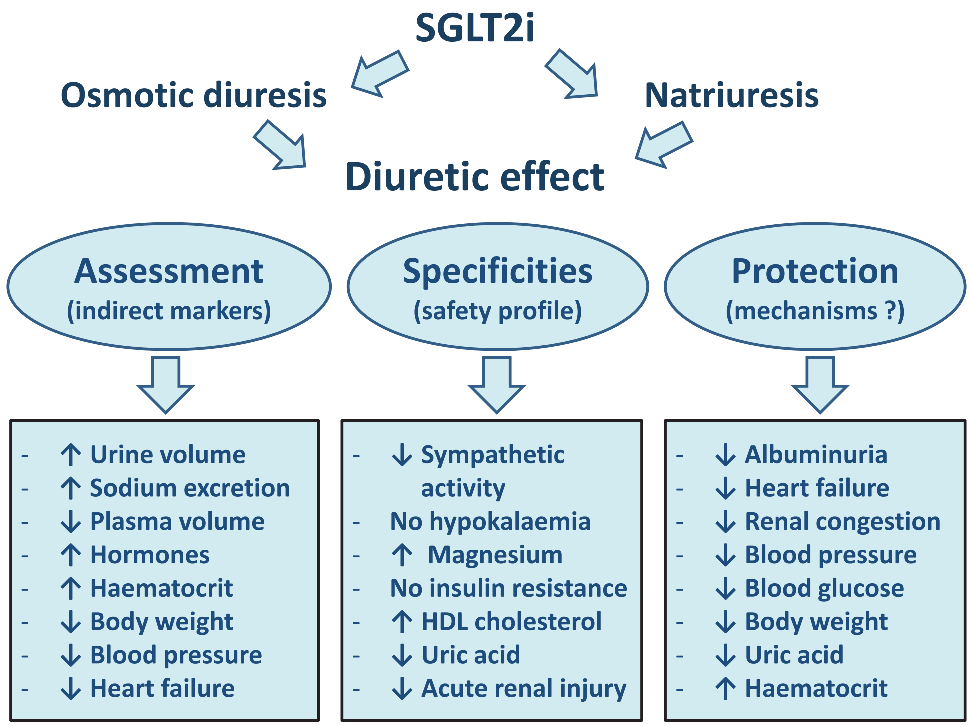

Fig. 1. Diuretic effect of SGLT2is: assessment, specificities and hypothetical mechanisms for renal protection.

discuss the potential mechanisms by which a diuretic effect of SGLT2is could contribute to improve renal outcomes (Fig. 1).

Assessment of a diuretic effect

Studying the diuretic effect of a drug is not so convenient, and the results of studies with SGLT2is, mostly using indirect estimations, were not concordant.

Measurement of urine volume and natriuresis

The most basic approach to demonstrate a diuretic effect is to show a significant increase in urine volume and/or urinary excretion of sodium. Regarding the effect of SGLT2is on these variables, results are not uniform [18, 19]. Some authors showed a significant increase in urine volume (~100 to 500 mL/24 h) [20–28] while others did not (or found a non-sustained effect) [29–34]. Similarly, some investigators reported an increase in urinary sodium excretion [21, 22, 35, 36], while others did not (or found a non-sustained effect) [20, 26, 28-33, 37, 38]. Discrepancies between studies could be explained by differences in study design (duration of follow-up, standardised diet regarding sodium intake or not, control of fluid intake or not), subject characteristics (healthy subjects with normal renal function versus diabetic patients versus patients with chronic heart failure or renal disease), or concomitant potentially interfering drugs as background therapy (no co-medications versus inhibitors of the renin-angiotensin-aldosterone system [RAAS] versus thiazides or loop diuretics). It can be anticipated that a diuretic effect is more easily demonstrated in patients with heart failure (and potential fluid overload) than in healthy subjects or diabetic patients without chronic kidney disease (CKD), in whom compensating mechanisms are rapidly activated when any diuretic is prescribed [39]. When added to RAAS inhibitors in patients with T2DM and albuminuria, but with a preserved estimated glomerular filtration rate (eGFR), dapagliflozin 10 mg exerted both osmotic and natriuretic diuretic effects, as reflected by increased urinary osmolality and fractional lithium excretion. However, as a result, compensating mechanisms were activated within 6–12 weeks, retaining sodium and water [36]. In patients with heart failure, SGLT2is will likely be co-prescribed with a loop diuretic, but this combined effect is not well-defined. The RECEDE-CHF trial showed that empagliflozin 25 mg caused a significant increase in 24-hour urine volume without an increase in urinary sodium when used in combination with a loop diuretic in patients with T2DM and chronic heart failure, both at day 3 and week 6 [40]. In the similar people with T2DM and heart failure, ipragliflozin 50 mg had an acute natriuretic activity measured after 3 days; this effect was strongly predicted by lower first-morning urinary sodium excretion and higher dosage of loop diuretics at baseline. According to the authors, these findings might suggest that SGLT2is could restore responsiveness to loop diuretics in symptomatic patients with T2DM and heart failure [41]. Albeit, it becomes increasingly obvious that SGLT2is exert effects beyond just glucosuria, natriuresis and diuresis [2, 42, 43].

Reduction in plasma volume

A reduction in plasma volume may be considered as an indirect marker of a diuretic effect. However, measurement of plasma volume is not easy to perform. A mechanistic study performed in 14 patients with T2DM showed that dapagliflozin 10 mg does not impact plasma volume (measured by indocyanine green dilution method, which is not a reference method) [29]. Others studied a subgroup of a randomised controlled trial (RCT) over a 12-week period and measured plasma volume by an isotopic method (^{51}Cr-labelled erythrocytes, which is a true reference method) in 30 patients treated by placebo, hydrochlorothiazide 25 mg or dapagliflozin 10 mg. A median decrease of 7% in plasma volume was observed in the dapagliflozin group (whereas non-significant changes were shown in the two other arms), an effect that was sustained for at least 12 weeks [44]. However, in the same type of patients and over a similar 12-week period of treatment, other authors showed in a placebo-controlled study with canagliflozin 300 mg (n = 18 in each arm) that urine volume increased (+ ~160 mL/24) and plasma volume (measured by indocyanine green dilution method) decreased (−5%), after one week, yet the effect was not maintained after 12 weeks of therapy

[31]. A final study included 20 patients with T2DM and stable chronic heart failure in a cross-over, placebo-controlled design for a period of 14 days. Plasma volume was measured by ^{131}I albumin indicator dilution and was shown to be reduced (~−138 mL) with empagliflozin 10 mg [35].

Other studies argued for a decrease in plasma volume but the latter was only estimated by equations based on haematocrit and/or bodyweight changes. However, this approach is highly questionable knowing the "intrinsic" effects of SGLT2is on these two parameters, stimulation of erythropoiesis on the one hand and reduction in fat mass on the other hand [45, 46]. It has been suggested that the diuretic effect of SGLT2is could impact interstitial volume (or the extracellular water) more than effective blood volume, so potentially improving symptoms like lower limb oedema and/or lung fluid overload [47]. However, this interesting hypothesis was based on mathematical models [48, 49] or measurement of extracellular volume by bioimpedance in limited samples of patients [24, 50, 51]. Using a bioimpedance method in a comparative study in patients with CKD, Ohara and colleagues reported a smaller reduction in extracellular water with dapagliflozin 5 mg compared with furosemide (mean dose 55 mg/day). Both drugs had similar effect on intracellular water, but a smaller reduction of the ratio extracellular water on total body water was observed with dapagliflozin. These findings suggested that in comparison with furosemide, the dapagliflozin effect on extracellular volume was not associated with intravascular volume depletion [24]. The same group showed that pre-treatment extracellular volume status predicts body fluid response to dapagliflozin in patients with T2DM and CKD. The authors hypothesised that the diminished extracellular fluid reduction by the SGLT2i in patients without severe extracellular fluid retention may contribute to maintaining a suitable body fluid status [51].

To our knowledge, no studies directly compared the risk of volume depletion, dehydration and hyponatraemia in patients treated with SGLT2is versus loop diuretics. Of note, in patients with heart failure from the DAPA-HF trial, adverse events related to volume depletion (yet not specified in the publication) occurred more frequently with dapagliflozin 10 compared to placebo, with more events seen in individuals on a diuretic background therapy and randomised to dapagliflozin [52]. If volume depletion could occur, it should be recalled that any-type renal adverse events and serious adverse renal events were less frequent in the treated group, a clinically relevant result discussed further in the present article [53].

Hormonal and haematocrit responses

Another indirect argument for a diuretic effect of SGLT2is may be derived from changes in compensatory hormonal responses or in haematocrit arguing for some haemoconcentration. Levels of plasma renin activity, serum angiotensin II and/or aldosterone may increase in patients treated by SGLT2is [19] but once again results were far from uniform across reported studies (and for some authors the effect was not sustained) [20, 28, 33, 36, 37, 44, 50, 54]. In a 12-week head-to-head comparative study, the increase in plasma renin activity was smaller with dapagliflozin 10 mg than with hydrochlorothiazide 25 mg while the rise in plasma aldosterone levels appeared similar in the two groups [44].

The increase of haematocrit with SGLT2is was interpreted by some investigators as reflecting plasma volume restriction [20, 27, 31, 35, 55]. However, this interpretation is still debated, as other investigators described increases of erythropoietin and/or reticulocytes levels, suggesting a direct effect of SGLT2is on erythropoiesis [35, 37, 56, 57]. It has been hypothesised that SGLT2is reduce the workload of the proximal tubules and improve tubulo-interstitial hypoxia, allowing "neural crest-derived" fibroblasts surrounding the damaged renal tubules to resume normal erythropoietin production [58].

Reductions in body weight

SGLT2is are consistently associated with a bodyweight loss of a few kilograms [59]. Although this weight reduction predominantly results from a reduction in fat mass as shown by several studies of body composition [60], a minor part might be attributed to some fluid loss resulting from the diuretic effect, especially soon after the initiation of SGLT2i therapy [50].

Reductions in arterial blood pressure

Diuretics are able to reduce arterial blood pressure and are commonly used in the treatment of hypertension, including in patients with T2DM [61]. SGLT2i therapy is associated with a significant and consistent reduction in arterial blood pressure, an effect more marked on systolic than on diastolic pressure (on average − 4/2 mm Hg) [62]. Post-hoc analyses of clinical trials across the spectrum of eGFR rates from 30 to 80 ml/min/1.73 m^2 demonstrated similar magnitudes of blood pressure reduction in spite of far less reduction in glucosuria amongst those with advanced CKD. Thus, sustained reduction in arterial blood pressure observed with SGLT2is appears to be multifactorial rather than due to osmotic diuresis only and natriuresis that is mostly transient [63]. Bodyweight loss, reduction in arterial stiffness and improved endothelial function could contribute to the lowering effect of arterial blood pressure [1].

Remarkable effect on heart failure

Indirect arguments for a diuretic effect of SGLT2is are coming from cardiovascular outcome trials themselves [6]. Indeed, many authors suggested that "only" a diuretic effect of SGLT2is could explain the large positive effect in terms of "hospitalisation for heart failure" (the most impressive "cardiovascular" effect reported with this pharmacological class) [4], whereas the effect on stroke, for example, was not present [6, 13, 14]. Furthermore, the reduction in the incidence of hospitalisation for heart failure appears rapidly after the initiation of SGLT2i therapy, within the first few weeks already, an early effect that argues for a predominant haemodynamic (diuretic ?) mechanism [4]. This effect has been recently confirmed in patients with and without T2DM who had heart failure with either reduced [7, 8] or preserved [9] left ventricular ejection fraction.

Specificities of SGLT2is compared to other diuretics

The family of diuretic compounds is heterogeneous but all of them may be associated with various adverse events [39, 64]. Of note, SGLT2is exert a diuretic activity (an osmotic diuresis probably associated with a certain degree of natriuresis) that appears to be unique [43, 65], with the major advantage of not being affected by most of the side effects reported with other diuretics [18].

Absence of sympathetic activation

In contrast to other classical diuretics, thiazides and loop diuretics, SGLT2is are not associated with an increase in sympathetic activity and heart rate [66]. On the contrary, reduced sympathetic activity has been reported with SGLT2is both in animal models [67] and in humans [68]. The main putative underlying mechanisms for these sympatholytic effects with SGLT2is have been recently reviewed [69].

Absence of ionic disturbances

Classical diuretics (thiazides, loop diuretics) are associated with a risk of hypokalaemia which can trigger cardiac arrhythmia, adverse cardiovascular events and increased risk of mortality [70, 71]. One potential major difference with these diuretics is that SGLT2is are not associated with a higher risk of hypokalaemia [72–74]. Recently, a post-hoc analysis of CREDENCE showed that canagliflozin was associated with a lower risk of hyperkalaemia in patients with T2DM and CKD treated with RAAS inhibitors, without increasing the risk of hypokalaemia [75].

Classical diuretics may result in some degree of hypomagnesaemia, which might be associated with various side effects [64]. In contrast, a significant increase in serum magnesium was reported with SGLT2is in patients with hypomagnesaemia [76], yet the clinical significance of this effect remains unclear. Of note, however, a recent prospective cohort study reported that serum magnesium level is inversely associated with heart failure and microvascular complications, including CKD, in patients with T2DM [77].

Absence of deleterious metabolic effects

The metabolic profile of SGLT2is (notably in terms of insulin resistance, glucose control, changes in serum uric acid and high-density lipoprotein cholesterol levels [1]) is much more favourable than that of classical diuretics [61, 78]. In contrast to thiazides which are associated with increased insulin resistance and associated disorders, especially when they are used at high dosage [61], SGLT2is reduced insulin resistance-associated metabolic disorders [79].

Hyperuricaemia may be increased by diuretics and is recognised as a risk marker for CKD [80]. In contrast, SGLT2is reduced serum uric acid levels [81]. It has been hypothesised that this effect may result from the increase in the urinary excretion rate of uric acid, due to the inhibition of uric acid reabsorption mediated by the effect of SGLT2is on the GLUT9 isoform 2, located at the collecting duct of the renal tubule [82].

Absence of increased risk of acute renal injury

Diuretic use may be associated with a risk of adverse events due to volume depletion [71], an effect that was not observed in patients treated with SGLT2is, at least those recruited in RCTs [83]. Of note, no significant increase in renal adverse events related to volume depletion was reported in large prospective RCTs with SGLT2is [1, 6]. In case of diuretic-induced hypovolaemia, the risk of acute kidney injury (AKI) is well-known, and this risk is still enhanced by the concomitant use of RAAS inhibitors [84]. In contrast, SGLT2is have not been shown to be associated with an increased risk of AKI [10, 85, 86], although these drugs were well prescribed in patients potentially at risk of this complication (including patients with heart failure) and concomitantly treated with RAAS inhibitors and/or diuretics [86, 87]. Overall, it has even been proposed that SGLT2is could be protective for AKI [10, 85, 86], also in patients with heart failure as those recruited in DAPA-HF [53]. In a post-hoc analysis of the latter study, renal adverse events were less common with dapagliflozin compared with placebo in patients not on a diuretic at baseline compared with no difference in those who received a background diuretic therapy (interaction P-value = 0.02) [52]. The interpretation of this finding remains unclear and should be confirmed in further studies.

The reduction in the risk of AKI observed with SGLT2is, which contrasted with previous observations with classical diuretics, might be viewed as an indirect argument "against" a relevant diuretic effect of this pharmacological class [18]. However, the at least neutral (and apparently protective) effect of SGLT2is regarding AKI can be explained by several mechanisms which are not in contradiction with some diuretic effect [88]. Briefly, the diuretic effect of SGLT2is without an added risk of AKI could be explained by *i*) the concomitant vasodilation effect of SGLT2is on the post-glomerular efferent arteriole [37]; *ii*) the diuretic effect predominantly focused on the extracellular volume [24, 47, 48]; and *iii*) a major effect of SGLT2is on de novo heart failure [4], which is known to be associated with AKI episodes (cardio-renal syndrome) [89, 90].

All in one, while the relevance of the diuretic effect is still debated, it is clear that SGLT2is have a more favourable safety profile compared to that of classical diuretics.

Contribution of the diuretic effect to renal outcome

SGLT2is have proven to be associated with more favourable renal outcomes [10], even in patients already well treated at baseline with RAAS inhibitors, another pharmacological class unanimously recognised for its nephroprotection [91]. While the role of a diuretic effect on heart failure outcome could be easily understood for SGLT2is, its potential role on renal outcomes might appear less obvious. The potential diuretic contribution in the renal protection needs to be better studied in dedicated mechanistic studies, but such investigations are methodologically challenging. The diuretic effect of SGLT2is could be proportionally more important in some patients, as those with heart failure and/or fluid overload [15, 35, 46, 47]. Whether the osmotic or natriuretic effect is predominant (or if they are just coexisting) is also a subject of debate [15, 35, 36, 49]. Because the osmotic glucosuric effect of SGLT2is is reduced in CKD patients, whereas the clinical (renal or cardiovascular) benefits remain in these patients, some authors are underlining the natriuretic effect, especially in the context of heart failure [15, 35]. Reasons for the renal benefits of SGLT2is are thus probably multiple, yet mutually not exclusive. Several underlying mechanisms, directly or indirectly associated with the diuretic effect, which could contribute to improve renal prognosis, will be briefly discussed.

Reduction in albuminuria

Increased urinary albumin excretion in patients with diabetic nephropathy is mainly due to an alteration in the glomerular filtration barrier, characterised by decreased podocyte number and function [2]. The presence of albuminuria within the glomerulus is toxic and elicits a sclerotic response that results in mesangial proliferation and glomerulosclerosis. In a meta-analysis of 41 eligible studies each 30% decrease in albuminuria reduced the risk of end-stage renal disease by 27% over a median follow-up of 3.4 years [92]. Thus, albuminuria may be considered as a self-perpetuating cause of diabetic nephropathy beyond a classical manifestation of the disease used for both diagnostic and prognostic purposes.

It must be reminded that diuretics (especially thiazides with their natriuretic effects) seem useful to decrease albuminuria in CKD patients, with a synergistic effect with RAAS inhibitors [93, 94]. The antiproteinuric effect of mineralocorticoid receptor antagonists has been clearly established through prospective and controlled studies [95]. The efficacy of other diuretics (loop diuretics) has been less explored, yet different investigations suggest that they might share similar antiproteinuric properties that should be evaluated further through controlled studies [95]. Of note, strong data on diuretics showing benefits on hard renal outcomes are lacking except for the mineralocorticoid receptor antagonist finerenone that recently showed a significant reduction in the risk of CKD progression in patients with T2DM [96, 97].

Several meta-analyses clearly showed that SGLT2is were associated with a significant reduction in albuminuria [98, 99]. Furthermore, the reduction in urine albumin-to-creatinine ratio (UACR) was more prominent in patients with moderately or severely increased albuminuria compared to those with only mild albuminuria [98, 99]. Thus, considering that albuminuria has been shown to be nephrotoxic [2], the consistent reduction in UACR reported with SGLT2is could contribute to their nephroprotective effects [95]. Following the findings of a strong association between reduction albuminuria and reduction in the risk of end-stage renal disease [92], the reduction in albuminuria with SGLT2is has been proposed as a marker for improved renal outcomes both in people with T2DM and in nondiabetic patients [100]. Recent subanalyses of large prospective RCTs have shown that the early antiproteinuric effect induced by SGLT2is predicts long-term preservation of kidney function [101, 102]. Nevertheless, a detailed analysis of available data suggests that the nephroprotection by SGLT2is is observed independently of the albuminuria level at baseline, even if a more marked effect may be observed in patients with very high albuminuria [11].

Positive effect on the cardio-renal syndrome

Expansion of extracellular fluid volume is central to the pathophysiology of heart failure. Therefore, diuretics, especially loop diuretics, are one of the cornerstones of therapy for heart failure. However, robust clinical trial evidence to guide the use of diuretics in patients with heart failure is sparse [103]. While loop diuretics have the benefit of legacy, SGLT2is increasingly seem to be more aligned to heart failure pathophysiology [65].

Acute heart failure is frequently associated with AKI episodes, known as the cardio-renal syndrome [89, 90]. SGLT2is by decreasing the episodes of acute heart failure would contribute to prevent AKI episodes. It is known that AKI episodes are associated with a cumulative risk for developing advanced CKD in diabetes mellitus, independent of other major risk factors of progression [104]. Thus, improving cardiac function would potentially have a positive impact on renal “chronic” outcomes (like serum creatinine doubling or need for dialysis). This observation could be especially relevant to explain the persistent positive effect of SGLT2is in patients with near-to-normal eGFR and normal levels of albuminuria.

Diuretic-induced decongestion in patients with heart failure can improve glomerular filtration rate by reducing renal venous pressure [105]. SGLT2i therapy could protect diabetic kidney disease from failing by improving latent renal congestion even without symptomatic heart failure [106].

Thus, the diuretic effect would be particularly interesting in patients with (or at high risk of) heart failure. In patients of the RECEDE-CHF trial with heart failure, empagliflozin caused a significant increase in 24-hour urine volume (yet without an increase in urinary sodium) when used in combination with a loop diuretic. However, in this study, cardiac or renal outcomes were not studied [40]. A post-hoc analysis investigated the relationship between heart failure diagnosis, use of loop diuretics, and outcomes in patients with T2DM enrolled in the EMPA-REG OUTCOME trial. Rates of adverse events related to renal function were greater in patients receiving a loop diuretic with or without heart failure compared to the other patients. Of note, however, these increases were observed in both groups treated with placebo and empagliflozin, with a numerically lower incidence in patients receiving empagliflozin compared with placebo [107].

However, the type of heart failure might impact the influence of SGLT2is on the development of hard renal outcomes as suggested by an intriguing recent observation [108]. Indeed, the effects of empagliflozin on the rate of hospitalisation for heart failure on the one hand and on a composite of renal major outcomes (i.e. profound and sustained decreases in eGFR or renal replacement therapy) on the other hand were indirectly compared in patients with heart failure characterised by either reduced [8] or preserved [9] left ventricular ejection fraction. Despite quite similar effects on the reduction of hospitalisation for heart failure and on the attenuation of eGFR decline during the follow-up in both studies, an impressive reduction (hazard ratio (HR) 0.51, 95% confidence interval (CI) 0.33−0.79) in the composite renal outcome was observed in EMPEROR-Reduced, which contrasted with a trivial reduction (HR 0.95, 95%CI 0.73−1.24) in EMPEROR-Preserved [108]. The significance and mechanistic interpretation of this finding are still unclear, even if differences in the disease pathophysiology and in patient’s profiles should most probably be involved. Obviously, further investigations are needed to first confirm and then explain these provocative observations.

Improvement of surrogate endpoints at least possibly related to a diuretic effect

SGLT2i therapy exerts pleiotropic effects that could improve renal outcomes, amongst which improvement of blood glucose control, weight loss, reduction in arterial blood pressure, decrease of serum uric acid, increase of haematocrit and renal oxygenation [1]. Some of these effects may be at least partially attributed to the osmotic diuresis that accompanied sustained glucosuria and at least transient natriuresis. However, each single effect could not explain the better renal outcome, yet a contribution of a combination of all of them together could not be excluded. It has been shown that renal protection occurs independently of glucose control in patients with T2DM [109, 110]. Another major argument against a predominant contribution of better glucose control with SGLT2is is that renal protection was also present in non-diabetic patients [12]. As previously discussed, the small reduction in arterial blood pressure in diabetic patients already well treated (RAAS inhibitors) and with well controlled hypertension (mean systolic blood pressure < 140 mm Hg at baseline) could not explain the observed renal protection reported in prospective outcome trials with SGLT2is [111].

Conclusion

The diuretic effect of SGLT2is remains debated and its potential role in the renal protection needs to be better studied in dedicated mechanistic studies, but such investigations are methodologically challenging. In all cases, the diuretic effect of SGLT2is has many specificities and overall is different from other classical diuretics, with no stimulation of the sympathetic activity, no hypokalaemia, a lower risk of AKI and a lowering of serum uric acid. One possible most probably underestimated mechanism to explain the positive effect on renal outcome may be a reduction in albuminuria, an effect reported with other diuretics and shared (and even amplified) by SGLT2is as shown in many RCTs and observational studies. Furthermore, the diuretic effect of SGLT2is may be proportionally more important in some patients, as those with heart failure and/or fluid overload. Therefore, a positive effect of SGLT2is on the cardio-renal syndrome may also be considered owing to the remarkable protection against heart failure consistently reported with this pharmacological class. However, according to a recent observation from the two EMPEROR trials, different protection by SGLT2is against composite renal outcome may occur in patients with heart failure and reduced versus preserved left ventricular ejection fraction. In conclusion, the underlying mechanisms of the renal benefits of SGLT2is are probably multiple, amongst which a diuretic effect, and all these effects are most probably mutually not exclusive.

Declaration of Competing Interest

The Authors declare the following conflicts of interest in relation to the content of this article.

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